REMARKS

Applicants submit the foregoing amendments and following remarks in response to the final Office Action dated February 28, 2005. Claims 42-51 remain pending, and new Claims 52-55 have been added. Thus, Claims 42-55 are presented for further examination.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Specifically, support for new Claims 52-55 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [0407], and Example 18 starting at paragraph [0529].

Applicants thank the Examiner for his review of the instant application, and request reconsideration of the application in view of the following remarks.

Rejection under 35 U.S.C. §101 – Utility

The PTO has maintained the rejection of the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO alleges that the invention is not supported by either a substantial asserted utility or a well-established utility.

The PTO states that while the data in Example 18 shows the nucleic acid is differentially expressed, there is no data for the polypeptide or any other nucleic acid other than SEQ ID NO:1 being differentially expressed in any tumor. The PTO's position is that the art is so unpredictable that a person skilled in the art would not be convinced that the asserted utility is true. The PTO relies on Chen et al. (Molecular and Cellular Proteomics 1:304-313, 2002) for the proposition that protein expression does not correlate with gene over-expression and thus the art is unpredictable. The PTO also cites from Genes VI, Benjamin Lewin, 1997, Chapter 29 – Regulation of Transcription, 1st page, which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription."

The PTO rejects the Grimaldi and Polakis declarations, arguing that while these declarations may show a correlation between mRNA and protein expression in some cases, "there are equally references that show this not to be the case" and that the references cited by the

PTO "underscore the unpredictability in the art as showing that protein expression does not correlate with gene over-expression." Office Action at 3.

In response to Applicants' argument that it is the accepted understanding in the art that there is a reasonable correlation between gene expression and protein expression, the PTO states that the Alberts reference provides support that not all genes would be expressed into protein and that there are numerous controls over gene expression. The PTO states that even though Applicants have provided some references that show that mRNA correlates with protein expression in some cases, the Examiner has cited other articles that show this not to the case, and therefore the art is unpredictable. Thus, the PTO maintains that there is no clear "reasonable" correlation between gene expression and protein production, and it is unpredictable whether the protein would be produced and therefore, the utility is not substantial.

Applicants respectfully traverse.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid or polypeptide is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

In addition, the mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1), gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ

885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). As Applicant's have previously pointed out, this is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants rely on *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985), which hold that the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly rectal and lung cancer. Applicants are not asserting that the claimed polypeptides necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO180 polypeptide is differentially expressed in rectal and lung tumors;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO180 polypeptide is increased in rectal tumor compared to normal rectal tissue, and in normal lung tissue compared to lung tumor, it is more likely than not that the PRO180 polypeptide is differentially expressed in rectal and lung tumor and is therefore useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO states that while the evidence reported in Example 18 shows differential expression of the nucleic acid, there is no data that the polypeptide is also differentially expressed;

2. The PTO cites Chen *et al.* and Genes VI for the proposition that gene expression and protein expression do not always correlate and thus the art is unpredictable;

3. The PTO asserts that even though Applicants have provided some references that show that mRNA correlates with protein expression in some cases, the PTO has provided other articles that show this is not the case. Thus, there is no clear "reasonable" correlation between gene expression and protein production.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants have submitted the declaration of J. Christopher Grimaldi, which establishes the reliability of the data of Example 18, and have provided sufficient evidence to establish the existence of a reasonable correlation between gene expression and protein expression. Second, the references provided by the PTO are not contrary to Applicants' arguments and evidence, and therefore do not support the PTO's position. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO180 protein is more likely than not differentially expressed in certain tumors. This provides utility for PRO180 and related proteins as cancer diagnostic tools.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.** Given the evidence provided by Applicants, those of ordinary skill in the art, would be convinced, **to a reasonable probability**, that the asserted utility is true.

Applicants have established that the Gene Encoding the PRO180 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the data in Example 18 do not establish a utility because the specification does not disclose any information on the level of expression, activity, or role of the PRO180 polypeptide in cancer. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed polypeptides related to the gene encoding the PRO180 polypeptide.

Applicants have previously submitted the declaration of J. Christopher Grimaldi. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable

difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO180 cDNA between rectal and lung tumor tissue and normal rectal and lung tissue. Therefore, it follows that expression levels of the PRO180 gene can be used to distinguish rectal and lung tumor tissue from normal rectal and lung tissue. The PTO has not offered any significant arguments or evidence to the contrary. As explained below, it is more likely than not that the PRO180 polypeptide is also differentially expressed in rectal and lung tumor tissue, and can therefore be used to distinguish rectal and lung tumor from normal tissue. This provides utility for the claimed polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that, in general, a change in the level of mRNA for a particular protein leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO180 polypeptide in rectal and lung tumor, it is more likely than not that the PRO180 polypeptide is differentially expressed, and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants have submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and previously submitted support this statement.

Applicants have also provided a copy of the declaration of Paul Polakis, Ph.D., also an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "**such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.**" (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (previously submitted). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or <u>most genes</u> transcriptional controls are paramount. This makes sense because, of all the possible

control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

Further support is found in the fourth edition of Alberts et al., which has been previously discussed. In this reference, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Page 302 (emphasis added). Similarly, Figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Page 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount."

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, which has been previously submitted. Of the samples tested, 81 out of 87 showed "a high degree of correlation between PSCA protein and mRNA expression." The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a

promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor."

Further support can be found in Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), which states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO180 mRNA is expressed at a higher level in rectal tumor and normal lung compared to normal rectum and lung tumor, the PRO180 polypeptide will have the same expression pattern. This differential expression of PRO180 and related polypeptides make them useful as diagnostic tools for cancer.

In arguing against this assertion, the PTO cites two references. The PTO cites Chen *et al.* (Molecular and Cellular Proteomics 1:304-313, 2002) to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels and thus the art is unpredictable. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. This measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed polypeptides because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis.

Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO' s argument, which they do not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level

for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed herein, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene. Further, Chen et al. does not dismiss the value of mRNA expression patterns, and recognizes the value of both mRNA and protein expression as diagnostic tools: "[b]y combining proteomic and transcriptional analysis of the same samples, however, it may be possible to understand the complex mechanisms influencing protein expression in human cancer."

The citation from Genes VI relied upon by the PTO offers even less support for the PTO's position. The PTO relies on the statement that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." (Genes VI, Benjamin Lewin, 1997, Chapter 29 – Regulation of Transcription, 1st page). The PTO focuses on the portion of the statement that says "production of RNA cannot inevitably be equated with production of protein." What the PTO ignores is the portion of the statement that says "it is clear that the **overwhelming majority** of regulatory events occur at the initiation of transcription." This same reference states that transcription of a gene "is a major control point: probably **it is the most common level of regulation**." Id., emphasis added. This reference provides additional support for Applicants' position that that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein. Again, the correlation need not be necessary, invariable or exact, but merely "reasonable." *See Cross*, 753 F.2d at 1050. A reasonable correlation can be relied on to establish utility. Applicants have established this reasonable correlation.

The position of the PTO is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere

identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

Applicants submit that a lack of known role for PRO180 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of PRO180 is a cause or result of the rectal or lung tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO180 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that action taken in other applications is not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 2 and 3.)

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

> utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has offered Chen et al. and the excerpt from Genes VI to establish that the art is unpredictable and that one of ordinary skill in the art would reasonably doubt that the disclosed polypeptide is differentially expressed in certain tumors and can be used as a diagnostic tool. Applicants have provided arguments as to why these cited references fail to support the PTO's position. Thus, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement; and even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly rectal and lung cancer.

Applicants have established that the general understanding in the art, as shown by excerpts from leading textbooks in the field and supported by the Declarations of two experts in the field, as well as several additional references, is that mRNA expression more likely than not corresponds to protein expression. While the PTO cites an individual case where there is a lesser showing of correlation, this is an exception to the general understanding and expectation of those of skill in the art. The PTO states that it has cited references to establish unpredictability in the art. Applicants respond that its references are leading textbooks in the field, supported by the declarations of two experts, and numerous other references. The PTO cites exceptions to the general understanding in the art – this is insufficient to establish that those of ordinary skill in the art would disregard the general understanding established by Applicants and doubt the asserted utility.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO180 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO180 polypeptide is expressed at least two-fold higher in rectal tumor and normal lung tissue compared to normal rectum and lung tumor, respectively. Applicants have also established that the general understanding in the field is that there is a correlation between gene expression and protein expression. Thus, Applicants have provided strong evidence that the PRO180 gene and polypeptide are associated with rectal and lung tumors. Contrary to the assertions of the PTO, Applicants submit that they have provided sufficient evidence associating the PRO180 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly rectal and lung tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) there is no data showing differential expression of the PRO180 polypeptide in certain tumors; (2) the literature demonstrates that gene expression and protein expression do not always correlate; and, (3) because there is no clear, reasonable correlation between gene expression and protein expression, the claimed polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO180 gene in rectal tumor and normal lung tissue compared to normal rectal and lung tumor tissue, are real and significant.

Second, Applicants submit that excerpts from leading textbooks in the field, supported by the second Grimaldi Declaration and the Polakis Declaration and the references discussed above, demonstrate that it is well-established in the art that a change in mRNA levels *generally*

correlates to a corresponding change in the encoded protein levels. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Third, Applicants have shown that the references relied on by the PTO, Chen et al. and Genes VI, do not support the PTO's position that one of skill in the art would reasonably doubt the asserted utility.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO180 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic agents. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO180 set forth in the specification. Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis

in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO has maintained its rejection of Claims 42-51 under 35 U.S.C. § 112, first paragraph. The PTO states that since the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the rejection under 35 U.S.C. § 101 above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112, first paragraph.

In addition, the PTO maintains the rejection of Claims 42-43 and 50-51 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. According to the PTO, the specification does not describe polypeptides that are 95-99% identical to SEQ ID NO:2, wherein the nucleic acid is overexpressed. "One would not know how to make or use such molecules." Office Action at 7.

As amended, the pending claims are to polypeptides that have at least 95% or 99% amino acid sequence identity to the recited sequence and are "more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively" or the "isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples."

Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:2. Applicants have disclosed how to determine if the claimed

polypeptides or encoding nucleic acids are differentially expressed in rectal tumors or normal lung compared to normal rectum or lung tumor. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO:2, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO:2 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO180 gene and polypeptide are differentially expressed in rectal and lung tumors such that they can be used as cancer diagnostic tools. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in rectal and lung tumors. Other claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and "said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal and lung tissue samples," are also useful diagnostic tools. Because the polypeptide of SEQ ID NO:2 is more likely than not likely differentially expressed in rectal and lung tumors, antibodies for specific detection of this polypeptide in rectal and lung tissue samples are useful diagnostic tools.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112 – Written Description

The PTO has maintained its rejection of Claims 42-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO maintains that applicants do not describe any polypeptide having 95% or 99% identity to SEQ ID NO:2 or its extracellular

domain which is overexpressed in rectal tumors or normal lung. Just because one teaches how one could potentially obtain such a molecule does not give one possession of the molecule. There is no indication that such a molecule exists or what the structure of the molecule would be. The specification does not describe any other nucleic acid that encodes any polypeptide that is 95-99% identical to SEQ ID NO:2 which is encoded by a nucleic acid that is over-expressed in rectal tumors.

The Legal Standard for Written Description

Applicants have previously set forth the well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph: whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:2, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal and lung tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:2. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in rectal or lung tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids

or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502 which are attached hereto as Exhibits 4-9.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:2, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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